

REMARKS

Claims 1, 5-9, 11-15, 20-25, 27, 29, 31-33, 35-39, 41, 42, 44-49, 51-59 and 61 are being examined and all stand rejected. Claims 11-13 and 15 have been canceled without prejudice and subject to being re-asserted in a subsequent application.

Rejection Under 35 U.S.C. 103

Claims 1, 5-9, 11, 13, 15, 20-25, 27, 29, 31, 33, 35, 38, 39, 41, 44-49, 51-53, 55 and 56 were rejected in ¶13 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)).

In rejecting claim 1, and the claims dependent therefrom, the Examiner relies on the Lizardi '033 patent as teaching "a method of amplification comprising contacting multiple single-stranded non-circular random oligonucleotide primers (P1), one or more amplification target circles (ATCs), a DNA polymerase and multiple deoxynucleoside triphosphates (dNTP), under conditions promoting said contacting, wherein an ATC hybridizes to a plurality of P1 primers, wherein said conditions promote replication of the amplification target circle by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products and wherein at least one such dNTP renders the TS-DNA resistant to nuclease activity following incorporation thereinto...." (see Office Action at page 5, ¶6A).

In response, Applicants note that Lizardi does not teach multiple primers bound to a single ATC and, in fact, specifically teaches away from this. The basic teaching of claim 1 is not taught by Lizardi '033 patent, either alone or in combination with the other references. Applicants' claim 1 is directed to a method of amplification that requires

binding of multiple primers to a single amplification target circle. This is not taught or even suggested by Lizardi or any of the other cited references, alone or in combination.

Claim 1 recites specifically "wherein an ATC hybridizes to a plurality of said P1 primers" and the Examiner indicates that this limitation is taught by Lizardi but Applicants do not find such a teaching therein.

Claim 1 of the application recites, in pertinent part, "wherein an ATC hybridizes to a plurality of said P1 primers," meaning that the process generates an ATC that is hybridized to multiple P1 primers and whose amplification therefor produces multiple tandem sequence DNA products. This is not taught by Lizardi or any of the other cited references, either alone or in combination.

For example, the Examiner mentions that "Applicants admit that Lizardi teaches a secondary primer binding to a secondary ATC in Fig. 12." (see office action at page 2, last sentence) While this is certainly true, Applicants do not see how a secondary primer bound to a secondary ATC, wherein "secondary" refers to a subsequent amplification, translates into multiple primers bound to a single ATC. The latter is certainly not depicted in Fig. 12 of Lizardi. In fact, the secondary ATC (or Lizardi's open circle probe) of Fig. 12 is bound to the primary ATC and to a single primer, which is not the same as multiple primers on a single ATC, i.e., the primary ATC is not acting as a primer for anything.

The Examiner also claims that, "As admitted by Applicants, the secondary and tertiary primers have binding sites on the ATC, but, for reasons Applicants do not disclose, are forbidden to bind to it, even though they bind to TS-DNA sequences, which are exact replicas of the ATCs. " (see office action at page 3, lines 13-16)

In response, Applicants in no way say that these secondary and tertiary primers cannot bind to the ATC but only that a single such primer would bind at a given time in

the teaching of Lizardi. The Examiner is quite correct in observing that the TS-DNA sequences are replicas of the ATC but the TS-DNA is not an ATC but a linear structure. Lizardi nowhere shows a single ATC bound simultaneously to multiple primers.

Indeed, Lizardi teaches away from multiple primers on a single circle. Thus, Lizardi states in pertinent part that,

"The primer complement portion is part of the spacer region of an open circle probe. The primer complement portion is complementary to the rolling circle replication primer (RCRP). Each OCP should have a single primer complement portion. This allows rolling circle replication to initiate at a single site on ligated OCPs." [emphasis added] [see Lizardi '033 patent at column 6, lines 48-53]

If each ATC, or circle, or OCP, or whatever one wants to call the template, is to have "a single primer complement portion" for binding the primer then logically this template can bind only a single primer at a given time. Lizardi forms his circular template by ligation of the OCP ("as used herein the term amplification target circle includes ligated open circle probes." – see Lizardi '033 at column 9, lines 48-51) and, as he says in the above excerpt, replication is initiated at a single site on ligated OCPs.

Whether or not subsequently produced TS-DNA product can bind multiple primers is not relevant to Applicants' invention since TS-DNA is not an ATC but contains only tandem repeats of the ATC sequence. Likewise, the use of secondary and tertiary ATCs is irrelevant so long as no single circle binds to multiple primers. In sum, Lizardi never shows a single circle template (whether primary, secondary or tertiary) bound to more than a single primer at any one time – only Applicants teach this.

In the interest of clarity, Applicants have amended claim 1 to recite this simultaneous binding of multiple primers to a single ATC molecule. No other claims have been amended. Applicant believes this adds no new matter and does not go

beyond what is in the pending claims so as to require any additional searching because, as Applicants have stated in their previous response, "In this way multiple extensions are achieved simultaneously from a single amplification target circle." (see application at page 6, lines 7-9) This means that more than one primer must be simultaneously bound to the same ATC and none of the cited references, either alone or in combination, teach, or even suggest, such a method. (see Amendment of 24 November 2004 at page 17, lines 11-15)

Applicants have also amended claim 1 to recite that the ATC is single-stranded, a limitation originally contained in pending claim 11, and have canceled claims 11-13 and 15. Applicants have also suitably amended claim 24 so as to limit this to use of a single stranded ATC in keeping with amended claim 1.

The Landers reference is relied on as showing the use of YACs with multiple primers. However, such YACs are duplex in nature and thus combination with Lizardi would require some type of nicking process to initiate replication, a step not recited by Applicants in claim 1. Because combination of Lizardi and Landers would require use of an additional step not taught by Applicants, their combination cannot achieve the invention of claim 1. Thus, claim 1, and the other claims (all of which depend directly or indirectly from claim 1, are believed patentable over any combination of these references.

The rejection also relies on Eckstein et al as teaching use of exonuclease III (with 3'-5'-exonuclease activity) and 3'-phosphorothioate as a means of preventing exonuclease degradation. In response, Applicants contend that combination of such teaching with that of Lizardi and Landers does not achieve the invention of claim 1 because Eckstein only teaches use of specific enzymes and specific nucleotides which, if combined with the other references, does not produce a method of

amplification involving a single ATC bound simultaneously to multiple primers, regardless of the nucleotides incorporated or the particular enzyme used. In effect, because Lizardi and Landers together cannot achieve Applicants' claimed invention, combination with Eckstein to use particular enzymes or nucleotides does not succeed either. Thus, all three references, individually or in combination, do not achieve the invention of Applicants' claim 1.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claim 1 and claims dependent therefrom be withdrawn.

Claims 12, 36 and 37 were rejected in ¶14 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Rothberg et al (U.S. Pat. No. 6,274,320).

Here, the first 3 references are relied upon for rejection as already discussed while Rothberg et al is cited to show use of a solid support. In response, Applicants reiterate their above comments (without lengthy analysis) and urge that because claims 12 and 36 depend from claim 1, and claim 37 depends from claim 36, these claims are likewise patentable as is claim 1 irrespective of the Rothberg et al reference, which only adds the limitation of using a solid support. Because claim 1 is patentable over the 3 basic references, it must be patentable when an additional limitation is added. In sum, combination of a solid support with the first 3 references does not achieve a single stranded ATC bound simultaneously to a plurality of primers and thus claim 1 and all claims dependent from it are patentable over the combination of these 4 references.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 12, 36 and 37 be withdrawn.

Claims 14, 57 and 58 were rejected in ¶15 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Navarro et al (J. Virol. Meth., Vol. 56, pp. 59-66 (1996)).

Navarro et al is cited for use of RNA viroids. However, claims 14, 57 and 58 depend directly or indirectly from claim 1 and, because claim 1 is patentable over the 3 basic references, addition of Navarro et al adds little (and is irrelevant to claim 1 *per se*). Thus, the 3 basic references fail to teach use of a single stranded ATC with multiple primers bound simultaneously thereto (for the reasons already stated) and combination of the teaching of viroids with the other references does not achieve Applicants' claimed invention. Consequently, claim 1 is patentable is patentable when an additional limitation is added.

In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 14, 57 and 58 be withdrawn.

Claims 32, 42 and 59 were rejected in ¶16 of the Office Action as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033), Landers et al (U.S. Pat. No. 6,703,228) and Eckstein et al. (Trends in Bioch. Sci., Vol. 13(3), pp. 97-100 (1989)) and further in view of Skerra et al (Nucleic Acids Research, Vol. 20, pp. 3551-3554 (1992)).

Here, Skerra is cited for use of incorporation of a phosphorothioate nucleotide at the 3'-end of a primer to render it resistant to 3'-5' exonuclease activity of certain DNA polymerases. However, this limitation is not recited in claim 1, which is patentable over the 3 basic references for the reasons stated above, so that combination of the teaching of Skerra with the other references does not succeed in achieving Applicants' invention of amplification using a single stranded ATC bound simultaneously to multiple primers. If anything, combination of the basic 3 references with Skerra would only add a specific limitation that would not render claim 1 obvious.

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In view of all of the previous remarks, Applicants respectfully request that this ground of rejection as it applies to claims 32, 42 and 59 be withdrawn.

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